UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,955	02/06/2006	Gerd Haberhausen	21518-US	2633

22829 7590 12/24/2008

Roche Molecular Systems, Inc.
Patent Law Department
4300 Hacienda Drive
Pleasanton, CA 94588

EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
12/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,955	HABERHAUSEN ET AL.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 8-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/12/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. The amendment filed September 29, 2008 has been entered. Claims 1-5 and 8-10 have been amended. Claims 6-7 have been cancelled. Claims 1-5 and 8-10 are under consideration in this office action.

Withdrawal of Objections and Rejections

2. The following objections and rejections have been withdrawn in view of applicants' amendment:

a) The objection of claim 1-10; and

b) The rejection of claim 3 under 35 U.S.C. 112, second paragraph.

Response to Arguments

3. Applicant's arguments filed September 29, 2008 have been fully considered but they are not persuasive.

Double Patenting

4. The examiner acknowledges applicants consideration of filing terminal disclaimers with respect to provisional obviousness-type double patenting rejections over application 10/534,915 and 10/534,319. However, the provisional obviousness-type double patenting rejections over claims 1, 2, 4, 6, 8 and 9 on the ground of

nonstatutory obviousness-type double patenting as being unpatentable over copending Application No. 10/534,915 and 10/532,319 are maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Jannes et al., (WO 96/00298).

Claim 10 is drawn to a kit for the identification of a pathogenic Gram positive bacterium or a subset of pathogenic Gram positive bacteria selected from the genera *Enterococcus, Staphylococcus* and *Streptococcus*, and containing a comprising: a) at least one set of amplification primers capable of amplifying a pre-selected nucleic acid sequence comprising of at least 20 nucleotides of the 16S/23S rRNA spacer region of *Enterococcus, Staphylococcus* or *Streptococcus,* b) at least one internal control template, and c) at least one hybridization reagent capable of detecting said pre-selected nucleic acid sequence, wherein said amplifying and detecting are performed in one reaction vessel.

Jannes et al., teach kits for detection of at least one organism in a sample were primers are used which enable the detection of a particular panel of organisms selected

from the genera *Staphylococcus, Enterococcus* and *Streptococcus* (page 5, lines 13-24). Jannes et al., teach sequences of 16S-23S rRNA spacer regions to derive useful primers (page 5, lines 11-12). Jannes et al., also teach primers as specified in Table 1b. Jannes et al., teach detection and identification of the target material can be performed by using one of the many electrophoresis methods, hybridization methods or sequencing methods described in literature and currently known by men skilled in the art (page 13, lines 19-21). Jannes et al., teach assays applying oligonucleotide probes, including negative or positive control oligonucleotides (page 13, lines 25-26). Jannes et al., teach that it should be clear that any other hybridization assay, whereby different probes are used under the same hybridization and wash conditions can be used for the above-mentioned detection and/or selection methods (page 15, lines 7-9).

Therefore Jannes et al., teach the instant invention.

Response to Arguments

6. Applicant's arguments have been fully considered but they are not persuasive.

Applicants argue that the claims additionally require "wherein said amplifying and detecting are performed in one reaction vessel;" therefore Jannes et al., do not anticipate the claim. Regarding the interpretive "wherein" clause recited in claim 10, the clause does not recite any additional components for the kit. Rather the "wherein" clause simply states a characterization or conclusion of the amplifying and detecting results. Therefore, the "wherein" clause is not considered to further limit the kit defined by claim 10 and has not been given weight in construing the claims. See *Texas*

Instruments Inc. v. Int 'l Trade Comm 'n, 988 F.2d 1165, 1179, 26 USPQ2d 1018, 1029 (Fed. Cir. 1993).

Applicants argue that Examples 1-9 teaches method that require multiple reaction step and multiple reaction vessels. However, contrary to applicants' assertion Jannes et al., Example 3 discloses the amplification and detection occurring on the membrane test strip, which meets the limitation of one reaction vessel. Therefore applicants' arguments are not persuasive.

Applicants' argue that Jannes et al., does not recite at least one internal control template; therefore Jannes et al., do not anticipate the claim. However, Jannes et al., teach assays applying oligonucleotide probes, including negative or positive control oligonucleotides. Furthermore, the instant application states that control templates comprise a known sequence with a primer binding site complementary to at least one set of amplification primers. Jannes et al., clearly disclose the use of primers with a known sequence with a primer binding site complementary to at least one set of specific amplification primers. Therefore applicants' argument is not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-6 and 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jannes et al., (WO 96/00298) in view of de Silva et al., (Biochemica. 1998. No. 2:12-15).

The claims are drawn to a method for identification of a pathogenic Gram positive bacterium or a subset of pathogenic gram positive bacteria from a predetermined group of pathogenic Gram positive bacteria in a clinical sample comprising: a) providing said clinical sample containing at least partially purified nucleic acid, b) subjecting said clinical sample to at least one amplification step and at least one detection step in one reaction vessel, said steps comprising: ba) at least one set of amplification primers capable of amplifying a pre-selected nucleic acid sequence comprising at least 20 nucleotides of the 16S/23S Spacer region from a predetermined sub-group of pathogenic Gram positive bacteria to which said Gram positive bacterium or subset of pathogenic Gram positive bacteria belong, bb) at least one internal control template, and bc) at least one hybridization reagent capable of detecting said pre-selected nucleic acid sequence from said predetermined sub-group of pathogenic Gram positive bacteria, further comprising bca) monitoring hybridization of said hybridization reagent at a pre-selected temperature, said hybridization being indicative for the presence in

said clinical sample of at least one species contained in said predetermined sub-group, and bcb) monitoring temperature dependence of hybridization, said temperature dependence being indicative for the presence of at least the species of said pathogenic Gram positive bacterium or said subset of pathogenic Gram positive bacteria, wherein said pathogenic Gram positive bacterium or subset of pathogenic Gram positive bacteria is identified based on the results of the monitoring steps in bca) and bcb).

Jannes et al., teach a method of amplification and detection of one or several pathogenic organisms, specifically bacteria, through the detection of the rRNA spacer region (abstract). Jannes teaches a method for identification of a pathogenic organism from a predetermined group of pathogens, comprising: a) at least partially purifying nucleic acid from a clinical sample (Example 3, p. 78-83; alternatively, see Example 4, p. 84-86, p. 85 where clinical isolates were tested, see Table 7), b) subjecting said clinical specimen to at least one amplification step and at least one detection step, comprising: ba) an amplification step using at least one set of amplification primers capable of amplifying a pre-selected nucleic acid sequence comprising region from a predetermined sub-group of pathogenic Gram-positive bacteria to which said gram positive pathogenic bacteria belong (p. 82-83 or p. 85, bb) a detection step using at least one hybridization reagent capable of detecting a pre-selected nucleic acid sequence region from said sub-group of pathogens (p. 82-83 or p. 85, where clinical isolates were amplified using biotinylated primers and hybridized to 16s/23s rRNA spacer sequences in a reverse hybridization assay, see Table 5, 6 or 7 for hybridization results), said detection step bb) further comprising: bba) monitoring

hybridization of each of said hybridization reagents at a pre-selected temperature, said hybridization being indicative for the presence in the sample of at least one species contained in the sub-group (p. 82-83 or p. 85, where clinical isolates were amplified and hybridized to 16S/23S rRNA spacer sequences in a reverse hybridization assay, see Table 5, 6 or Table 7, where a variety of pathogens within a group were distinguished), and identifying the organisms or subset of organisms based on the results of step bb).

Jannes et al., teach clinical samples such as ones originating from the respiratory tract, cerebrospinal fluid, urogential tract, gastro-intestinal tract and food and environmental samples (pages 3-4, lines 24-7). Jannes et al., teach a method of detection and identification of particular taxons, genus, subgroups, species, subtypes, serovars and the like (page 4, lines 7-11). Jannes et al., teach a rRNA spacer region that is at least 20 nucleotides present in one or multiple copies of almost all eubacterial organism (page 2, lines 12-15).). Jannes et al., teach the identification of *Listeria, Mycobacterium, Streptococcus, Staphylococcus aureus* (page 4, lines 11-24 and page 5, lines 2-3). Jannes et al., teach an embodiment wherein gram positive pathogenic organisms are exclusively identified by said first amplification and detection reaction, Example 3, p. 78, where *Listeria*, a gram positive organism is detected. Jannes et al., teach the use of a predetermined group including *Staphylococcus aureus, Streptococcus pneumoniae* (page 24, lines 1-7; page 25, lines 1-7). Table 6 shows predetermined groups having *Enterococcus faecalis* and *Enterococcus faecium*. Example 9 and Table 9 show taxa tested. However, Jannes et al., do not explicitly

teach step bcb, wherein the temperature dependence of hybridization is monitored as indicative for at least the species of said pathogen.

de Silva et al., teach an embodiment comprising bcb) monitoring temperature dependence of hybridization, said temperature dependence being indicative for at least the species of said pathogen (p. 14, Figures 3 and 5, where an example of monitoring temperature dependence of hybridization is depicted). de Silva et al., teach fluorescence monitoring of amplification using hybridization probes based upon signals generated by FRET offers advantages over other techniques because its linear responses over a large dynamic range (page 12). Once amplification and FRET occur, a melting curve is generated that allows for rapid genotyping (page 13). de Silva et al., teach continuous fluorescence monitoring of the reaction as temperature is raised (page 13). de Silva et al., teach that changes can be easily distinguished suggesting that the fluorescence method is suitable for all single base mismatches (page 13). de Silva et al., teach a sensitive system that allows a single template copy to be distinguished and fluorescent probes that obtain the strongest signals (page 14-15).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to extend the methods as taught by Jannes et al., and incorporate the method of determining and monitoring the temperature dependence of hybridization as taught by de Silva et al., in order to arrive have the advantages over other techniques because of FRETs linear responses over a large dynamic range at the claimed invention. One of ordinary skill in the art at the time the invention was made would have been motivated to extend the methods taught by Jannes et al., and

incorporate the method of determining and monitoring the temperature dependence of hybridization as taught by de Silva to arrive at the claimed invention with in order to provide a more sensitive system having stronger signals. Furthermore, all of the claimed elements were known and disclosed by Jannes et al., and de Silva et al, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Response to Arguments

8. Applicant's arguments have been fully considered but they are not persuasive.

Applicants assert that de Silva does not teach the use of an internal control template as required in presently amended claim 1. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). However, Jannes et al., teach assays applying oligonucleotide probes, including negative or positive control oligonucleotides. And applicants instant specification state that details of using internal standards, particularly for quantification are well known in the art and were previously disclosed in EP 0 497 784 (dated August 12, 1992). Therefore, the inclusion of internal controls was not only already well known in the art, but also disclosed by Jannes et al., in view of de Silva et al. Therefore applicants' argument is not persuasive.

Furthermore, applicants argue that the amplification and detection are each performed by an additional set of amplification reagents in a separate reaction vessel than the detection of the primary target of interest (Factor V Leiden) cannot be considered an internal control template as defined by the instant application (see page 18 lines 23-31 in the application as filed). However, page 18, lines 23-31 do not state that internal controls cannot be in a separate reaction vessel. Rather the instant specification states that usually, control templates comprise a known sequence with a primer binding site complementary to at least one set of amplification primers. De Silva et al., clearly disclose the use of primers with a known sequence with a primer binding site complementary to at least one set of specific amplification primers. Therefore applicants' argument is not persuasive and the rejection is maintained.

Applicants assert that the probes as provided in Jannes were designed for a different purpose which is inherently different than the function required in a FRET-based system such as taught by de Silva. Contrary to applicants statement, Jannes et al., specifically states that Detection and identification of the target material can be performed by using one of the many electrophoresis methods, hybridization methods or sequencing methods described in literature and currently known by men skilled in the art (page 13). Furthermore, "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006,1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may

be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also *Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005)(reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component); *Celeritas Technologies Ltd. v. Rockwell International Corp.,* 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). Furthermore, nonpreferred and alternative embodiments constitute prior art. See M.P.E.P. 2123. Therefore, applicants argument that Jannes is limited to only teaching the line probe assay system is not persuasive, since Jannes et al., clearly discloses the use of any identification and detection system.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been *prima facie* obvious in view of the teachings of de Silva to monitor amplification

using melting curve analysis to establish melting temperature as claimed and potentially to apply the sequence specific probes used for detection of the rRNA spacer sequences to the fluorescent FRET format of amplification and detection because de Silva et al., teach that Jannes et al., methods for DNA analysis involving amplification of target regions by PCR and the visualization of hybridization were time-consuming and involve several handling steps that increase the risk of end product contamination and sample tracking errors, however the FRET techniques offers rapid real-time fluorescence monitoring, detection without the need for any post-PCR manipulations and allows high throughout genotyping and product quantification. Therefore, de Silva et al., clearly provides suggestions to combine the references.

Finally Applicants assert that there is a reasonable expectation of success in incorporating the methods of Jannes et al., and de Silva et al. However, Jannes et al., teaches labeling of nucleotides incorporated during the polymerase step of the amplification or by the use of labeled primers or by any other method known method. Therefore, the art provides a reasonable expectation of success, because the of the predictable outcome associated with the use of labeled hybridization probes wherein the proximity of the fluors allows resonance energy transfer.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-5, and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Neither the specification nor originally presented claims provides support for an claims are drawn to a method for identification of a pathogenic Gram positive bacterium or a subset of pathogenic gram positive bacteria from a predetermined group of pathogenic Gram positive bacteria in a clinical sample comprising subjecting said clinical sample to at least one amplification step and at least one detection step in one reaction vessel.

Applicant did not point to support in the specification for a method for identification of a pathogenic Gram positive bacterium or a subset of pathogenic gram positive bacteria from a predetermined group of pathogenic Gram positive bacteria in a clinical sample comprising subjecting said clinical sample to at least one amplification step and at least one detection step in one reaction vessel. Moreover, applicant failed to specifically point to the identity or provide structural characteristics of an amplification step and an detection step in one reaction vessel. Thus, there appears to be no teaching of an amplification step and an detection step in one reaction vessel.

Applicant has pointed to pages 11, lines 31; page 19, lines 23-31; and Example 1. Page 19, recites that in order to achieve sufficient specificity of the hybridization (i.e. to predominantly detect sequences of the target), the annealing temperature is selected such that the probes predominantly anneal/hybridize to the target nucleic acid(s), but not to nucleic acids of organisms not to be identified. Means to influence the selectivity of hybridization of probes to nucleic acids are widely known (length, GC-content and degree of complementarity). There is nothing in the passages that recites the amplification and detection steps being in one reaction vessels. Claim 7 is drawn to the steps being performed homogeneously. However, a homogeneous assay wherein all the components are present during measurement, is not equivalent to the amplification and detection steps being in one reaction vessel. Therefore, it appears that there is no support in the specification. Therefore, applicants must specifically point to page and line number support for the identity an amplification step and an detection step in one reaction vessel. Therefore, the new claims incorporate new matter and are accordingly rejected.

Conclusion

10. No claims allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/
Primary Examiner, Art Unit 1645